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IMPLEMENTATION OF THE INTERNATIONAL DRUG CONTROL TREATIES

CHANGES IN THE SCOPE OF CONTROL OF SUBSTANCES

Report of the Executive Director

Summary

The Commission on Narcotic Drugs has the responsibility under the international drug control treaties to decide what substances should be brought under international control and what control measures should be applied. Proposals for changing the scope of control of seven substances under the Convention on Psychotropic Substances of 1971 have been received from the Government of the United States of America and the Director-General of the World Health Organization. The Commission is called upon to decide what action may be required.

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Introduction

1. The international drug control treaties* provide that the responsibility for amending those treaties with respect to the substances under international control lies with the Commission on Narcotic Drugs. By deciding to add a substance to one of the schedules annexed to the 1961 or 1971 Convention or to one of the tables annexed to the 1988 Convention, the Commission creates an obligation for States parties to the relevant treaty to apply a specific control system to the substance at both the national and international levels. The Commission may also decide to delete a substance from a schedule or table, thereby removing it from international control, or to transfer a substance from one control system to another.

2. While the power to amend the schedules or tables of the 1961, 1971 and 1988 Conventions lies with the Commission (with the possibility of review by the Economic and Social Council at the request of a State party), the amendment procedure itself originates with a State Party or with either the World Health Organization (WHO) (for the 1961 and 1971 Conventions) or the International Narcotics Control Board (for the 1988 Convention); that procedure is set forth in detail in article 3 of the 1961 Convention, article 2 of the 1971 Convention and article 12 of the 1988 Convention.

3. At its thirty-eighth session, the Commission will have before it seven proposals relating to a change in the scope of control of substances under the 1971 Convention, one originally submitted by the United States of America and subsequently reviewed and assessed by WHO as required under the treaty, and six submitted by the Director General of WHO in exercise of the right and duty of that organization under the treaty.

I. CONSIDERATION OF NOTIFICATIONS RECOMMENDING SCHEDULING OR RESCHEDULING UNDER THE CONVENTION ON PSYCHOTROPIC SUBSTANCES OF 1971

A. Proposal to include methcathinone in Schedule I of the 1971 Convention

4. Pursuant to article 2, paragraph 1, of the 1971 Convention, the Government of the United States sent a notification to the Secretary-General informing him that, in its opinion, methcathinone (2-(methylamino)-1- phenylpropan-1-one) should be included in Schedule I of the Convention (see annex I). In accordance with the provisions of article 2, paragraph 2, of the Convention, the notification was transmitted by the Secretary-General to all Governments under cover of a note verbale dated 10 March 1994, with a request for comments and relevant information.

5. In accordance with the provisions of article 2, paragraph 2, of the 1971 Convention, the Secretary-General also transmitted a copy of the notification to WHO.

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* The Single Convention on Narcotic Drugs of 1961[1], that Convention as amended by the 1972 Protocol[2], the Convention on Psychotropic Substances of 1971[3] and the United Nations Convention against Illicit Traffic in Narcotic Drugs and Psychotropic Substances of 1988[4].

6. In response to the Secretary-General's request for additional information, replies had been received by the Secretariat of the Commission on Narcotic Drugs as of 20 September 1994 from the following 32 States: Andorra, Argentina, Australia, Bangladesh, Belarus, Cuba, Cyprus, Denmark, Ecuador, Finland, Germany, India, Japan, Jordan, Latvia, Maldives, Mexico, Namibia, Nepal, Nigeria, Norway, Oman, Pakistan, Saint Kitts and Nevis, Saudi Arabia, Spain, Switzerland, Syrian Arab Republic, Thailand, Turkey, Ukraine and Zimbabwe. The data submitted by Governments were communicated by the Secretary-General to the twenty-ninth meeting of the WHO Expert Committee on Drug Dependence, held at Geneva from 26 to 29 September 1994, and is summarized below for the information of the Commission.

7. Twenty-six of the respondents stated that methcathinone was not known locally and, therefore, did not pose any problem of abuse. Two Governments replied that methcathinone was a drug of abuse. Belarus reported 10-12 new cases of abuse per year. Latvia reported that methcathinone, known locally as ephedrone, was available and subject to national control, and was also one of the main drugs of abuse in that country. It should also be recalled that the information in support of the notification by the Government of the United States, proposing the scheduling of methcathinone, documented not only abuse, but also clandestine laboratories. Apart from the United States, no seizures or clandestine laboratories were reported by any Government.

8. In spite of the absence of widespread abuse, 14 Governments* expressed agreement with, or had no objection to, the proposal to include methcathinone in Schedule I of the 1971 Convention. Two Governments substantiated their position by specific comments. Saudi Arabia pointed out that methcathinone should be under international control because it was a synthetic analogue of cathinone and had even stronger effects on the central nervous system than cathinone. Switzerland indicated that it should be placed under control because it was a precursor for illicit manufacture of amphetamines.

9. The meeting of the Expert Committee referred to above in paragraph 6 examined the abuse potential of methcathinone and reported its findings to the Director General of WHO, resulting in the latter's recommendation, pursuant to article 2, paragraph 4, of the 1971 Convention, that the substance should be included in Schedule I of the Convention, in support of the proposal made by the United States. That recommendation is contained in the note from the Director General of WHO which is reproduced in annex II.

B. Proposals to include etryptamine in Schedule I, zipeprol in Schedule II, and aminorex, brotizolam and mesocarb in Schedule IV, and to transfer flunitrazepam from Schedule IV to Schedule III of the 1971 Convention

10. The Director General of WHO had informed the Secretary-General that the twenty-ninth meeting of the Expert Committee, in addition to examining the notification of the United States proposing the inclusion of methcathinone in Schedule I of the 1971 Convention (see paragraphs 4-9 above), would review a number of substances for possible control under the international drug control treaties.

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* Australia, Bangladesh, Cuba, Ecuador, Finland, Germany, Latvia, Nigeria, Pakistan, Saudi Arabia, Switzerland, Turkey, Ukraine and Zimbabwe.

11. During its meeting, the Expert Committee examined the abuse potential of a number of substances and recommended to the Director-General of WHO that six substances be brought under the control of the 1971 Convention. One of the substances was methcathinone (see paragraph 10); the other five were aminorex (2-amino-5-phenyl-2-oxazoline), brotizolam (2-bromo-4-(*o*-chlorophenyl)-9-methyl-6*H*-thieno[*3,2-f*]-*s*-triazolo[4,3-*a*][1,4]diazepine), etryptamine (3-(2-aminobutyl)indole), mesocarb (3-(*α*-methylphenethyl)-*N*-(phenylcarbamoyl)sydnone imine), and zipeprol (*α*-(*α*-methoxybenzyl)-4-(*β*-methoxyphenethyl)-1-piperazineethanol). The Expert Committee also recommended that flunitrazepam, which is currently in Schedule IV of the 1971 Convention, be transferred to another schedule of that Convention to ensure that stricter control measures apply to it.

12. Pursuant to article 2, paragraphs 1, 4 and 6, of the 1971 Convention, the Director-General of WHO notified the Secretary-General by a note dated 11 November 1994 that WHO was of the opinion that etryptamine should be included in Schedule I, zipeprol in Schedule II, and aminorex, brotizolam and mesocarb in Schedule IV of the 1971 Convention. WHO also recommended that flunitrazepam be transferred from Schedule IV to Schedule III of the 1971 Convention. The text of the notification, assessments and recommendations from the Director General of WHO are reproduced in annex II.

13. Following receipt of that notification, and in accordance with the provisions of article 2, paragraph 2, of the 1971 Convention, the Secretary-General sent to all Governments a note (NAR/CL.10/1994) dated 7 December 1994 in which he invited them to submit data on those substances concerning seizures or the existence of clandestine laboratories. Governments were also invited to indicate any economic, social, legal, administrative or other factors they might consider relevant to the question of the possible scheduling or rescheduling of those seven substances. Replies received from Governments to the note of the Secretary-General will be made available to the Commission in an addendum to the present document.

II. ACTION BY THE COMMISSION ON NARCOTIC DRUGS

14. The notification by the Director-General of WHO is now before the Commission for consideration in accordance with the provisions of article 2, paragraphs 5 and 6, of the 1971 Convention[3], which read as follows:

> "5. The Commission, taking into account the communication from the World Health Organization, whose assessments shall be determinative as to medical and scientific matters, and bearing in mind the economic, social, legal, administrative and other factors it may consider relevant, may add the substance to Schedule I, II, III or IV. The Commission may seek further information from the World Health Organization or from other appropriate sources.
>
> "6. If a notification under paragraph 1 relates to a substance already listed in one of the Schedules, the World Health Organization shall communicate to the Commission its new findings, any new assessment of the substance it may make in accordance with paragraph 4 and any new recommendations on control measures it may find appropriate in the light of that assessment. The Commission, taking into account the communication from the World Health Organization as under paragraph 5 and bearing in mind the factors referred to in that paragraph, may decide to transfer the substance from one Schedule to another or to delete it from the Schedules."

15. With regard to the decision-making process, the attention of the Commission is drawn to the fact that, article 17, paragraph 2, of the 1971 Convention[3] stipulates that "the decisions of the Commission provided for in articles 2 and 3 shall be taken by a two-thirds majority of the members of the Commission". From a practical point of view, this means that for a decision to carry, an affirmative vote of at least 36 members of the Commission is required. Because of this requirement, the Commission should vote separately on each substance. It should also be noted that a decision passed by consensus does not automatically ensure that a two-thirds majority of the members of the Commission have voted in favour of a proposal; it is accordingly necessary to vote by a show of hands, or by roll-call if requested by a State member of the Commission.

16. The Commission should therefore decide:

(a) Whether or not it wishes to include aminorex in Schedule IV of the 1971 Convention, or, if not, what other action, if any, is required;

(b) Whether or not it wishes to include brotizolam in Schedule IV of the 1971 Convention, or, if not, what other action, if any, is required;

(c) Whether or not it wishes to include etryptamine in Schedule I of the 1971 Convention, or, if not, what other action, if any, is required;

(d) Whether or not it wishes to transfer flunitrazepam from Schedule IV to Schedule III of the 1971 Convention, or, if not, what other action, if any, is required;

(e) Whether or not it wishes to include mesocarb in Schedule IV of the 1971 Convention, or, if not, what other action, if any, is required;

(f) Whether or not it wishes to include methcathinone in Schedule I of the 1971 Convention, or, if not, what other action, if any, is required;

(g) Whether or not it wishes to include zipeprol in Schedule II of the 1971 Convention, or, if not, what other action, if any, is required.

Notes

1. United Nations, Treaty Series, vol. 520, No. 7515.

2. Ibid., vol. 976, No. 14152.

3. Ibid., vol. 1019, No. 14956.

4. Official Records of the United Nations Conference for the Adoption of a Convention against Illicit Traffic in Narcotic Drugs and Psychotropic Substances, Vienna, 25 November-20 December 1988 (United Nations publication, Sales No. E.94.XI.5), vol.I.

Annex I

NOTIFICATION DATED 10 JANUARY 1994 FROM THE GOVERNMENT OF THE UNITED STATES OF AMERICA TO THE SECRETARY-GENERAL*

Subject: Addition of a substance to one of the Schedules annexed to the Convention

The Government of the United States of America, being a Party to the 1971 Convention on Psychotropic Substances, has information relating to the following substance which is not yet under international control, but which, in the Government's opinion, may require its addition to one of the Schedules of the 1971 Convention on Psychotropic Substances.

The Substance is known by the names of N-methylcathinone, methcathinone, ephedrone and monomethylpropion. Its chemical name is 2-(methylamino)-1-phenylpropan-1-one and its chemical formula is $C_{10}H_{13}NO$.

In the Government's opinion, the above substance should be added to Schedule I of that Convention.

The Government of the United States of America transmits this notification to the Secretary-General of the United Nations, in accordance with paragraph 1 of article 2 of the 1971 Convention on Psychotropic Substances, in order to initiate the procedure provided for under that article.

The relevant information in support of this notification is annexed hereto.**

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* Reproduced in the form in which it was received.

** Note by the Secretariat: The information submitted by the Government of the United States of America was transmitted to all States under cover of a note verbale (NAR/CL.1/1994) dated 10 March 1994 from the Secretary-General and accordingly is not reproduced here in extenso. Copies of that note verbale in English, French or Spanish are available from the Secretariat on request.

Annex II

NOTE DATED 11 NOVEMBER 1994 FROM THE DIRECTOR-GENERAL OF THE WORLD HEALTH ORGANIZATION TO THE SECRETARY-GENERAL*

The Director-General of the World Health Organization presents his compliments to the Secretary-General of the United Nations and has the honour to transmit, in accordance with article 2, paragraph 1, 4 and 6 of the Convention on Psychotropic Substances, 1971, assessments and recommendations of the World Health Organization, as set forth in the annex hereto, concerning proposed international control in respect of aminorex, brotizolam, etryptamine, flunitrazepam, mesocarb, meth*cathinone* and zipeprol.

The Director-General of the World Health Organization avails himself of this opportunity to renew to the Secretary-General of the United Nations the assurance of his highest consideration.

Aminorex

1. Substance identification

Aminorex (INN; CAS 2207-50-3), chemically 2-amino-5-phenyl-2-oxazoline, is also known as aminoxaphen and aminoxafen, and formerly as Apiquel and Menocil (aminorex fumarate). Aminorex has one asymmetric carbon atom in the molecule, so that two stereoisomeric forms and one racemate are possible.

2. Similarity to already known substances and effects on the central nervous system

Aminorex is chemically similar to 4-methyl*aminorex*, which is included in Schedule I of the Convention on Psychotropic Substances, 1971. Aminorex produces effects that are characteristic of central nervous system stimulants such as amfetamine, and was used clinically for its anorectic effects. Aminorex produces adverse effects similar to those produced by central nervous system stimulants. In addition, when used as an anorectic, aminorex was considered to have been responsible for the occurrence of a significant incidence of pulmonary hypertension. This led to its withdrawal from the market in 1968.

3. Dependence potential

In drug discrimination studies, aminorex generalized to amfetamine and cocaine. Animal self-administration studies indicate that aminorex has some reinforcing effects. These animal studies suggest that aminorex has a moderate dependence potential.

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* Reproduced in the form in which it was received.

4. Actual abuse and/or evidence of likelihood of abuse

Police and forensic reports indicate that aminorex is illicitly distributed in the United States of America as well as to a limited degree in Germany. These cases document the distribution of aminorex as amfetamine or metamfetamine on the street, suggesting that the population using the drug mainly comprises stimulant abusers. In spite of the limited level of actual abuse, aminorex is assessed to have a moderate abuse liability, taking into account the relative simplicity of its manufacturing in clandestine laboratories.

5. Therapeutic usefulness

Because of serious adverse effects, aminorex is assessed to have very little, if any, therapeutic usefulness.

6. Recommendation

Based on the available data concerning its pharmacological and toxicological profile, dependence potential and likelihood of abuse, the degree of seriousness of the public health and social problems associated with the abuse of aminorex is assessed to be significant. On the basis of this and the assessment of its therapeutic usefulness, it is recommended that aminorex be included in Schedule IV of the Convention on Psychotropic Substances, 1971.

Brotizolam

1. Substance identification

Brotizolam (INN; CAS 57801-81-7), chemically 2-bromo-4-(*o*-chlorophenyl)-9-methyl-6*H*-thieno[3,2-*f*]-*s*-triazolo[4,3-*a*][1,4]diazepine, is also known as Ladormin, Lendorm, Lendormin, Lindormin, Noctilan, Dormex and Sintonal.

2. Similarity to already known substances and effects on the central nervous system

Brotizolam produces pharmacological effects typical of the class of benzodiazepines. It binds with high affinity to benzodiazepine receptors. A number of studies have demonstrated the therapeutic effects of brotizolam as a short-acting hypnotic with a mean elimination half-life of 4-5 hours.

3. Dependence potential

Animal studies have shown that brotizolam has barbiturate type subjective effects. It produces alcohol-barbiturate type mild-to-severe withdrawal syndromes, and has some reinforcing effects. The few clinical studies available demonstrate the occurrence of rebound insomnia upon withdrawal of the drug. These findings collectively indicate that brotizolam has a moderate dependence potential similar to other benzodiazepine hypnotics.

4. Actual abuse and/or evidence of likelihood of abuse

In spite of its pharmacological similarity to other benzodiazepine hypnotics, and its marketing in 18 countries, actual abuse of brotizolam has been reported only in Germany and Hong Kong. In Germany, although there has been some abuse and illicit activity involving brotizolam, this was not considered serious enough to subject the drug to the

distribution control measures which are applicable to controlled drugs. In Hong Kong, following its introduction to the local market in 1988, the abuse of brotizolam increased rapidly among young people, leading to the application of stricter regulatory control measures in 1990. The company withdrew the product from the market in 1992.

Based on the experiences of Germany and Hong Kong with brotizolam, it is assessed that brotizolam has an appreciable abuse liability. The problem may be more acute in situations where prescription requirements for dispensing are not effectively implemented or are not applicable.

5. Therapeutic usefulness

Brotizolam is marketed as a hypnotic in 18 countries and may be considered to have a moderate to great therapeutic usefulness.

6. Recommendation

Based on the available data concerning its pharmacological and toxicological profile, dependence potential and likelihood of abuse, the degree of seriousness of the public health and social problems associated with the abuse of brotizolam is assessed to be significant, in cases where prescription requirements are not effectively implemented or required, a situation which exists in many developing countries. On the basis of this and the assessment of its therapeutic usefulness, it is recommended that brotizolam be included in Schedule IV of the Convention on Psychotropic Substances, 1971.

Etryptamine

1. Substance identification

Etryptamine (INN; CAS 2235-90-7), chemically 3-(2-aminobutyl)indole, is also known as *α*-ethyltryptamine and Monase. Etryptamine has a single chiral centre, so that two stereoisomeric forms and one racemate are possible.

2. Similarity to already known substances and effects on the central nervous system

Chemically, etryptamine is similar to hallucinogenic tryptamines, some of which are already in Schedule I of the 1971 Convention. Animal studies indicate that etryptamine produces effects similar to those produced by 3,4-methylenedioxy*metamfetamine* (MDMA), but its hallucinogenic effects are more pronounced than its stimulant effects. Like amfetamine, etryptamine increases locomotor activity in rodents. In a study using the behavioural pattern monitoring method, etryptamine significantly decreased investigatory behaviour, which is typical of hallucinogens and MDMA-like substances. The stimulant effects of etryptamine are slower in onset and more prolonged in duration than those of amfetamine. In addition, etryptamine inhibits monoamine oxidase.

In the early 1960s, etryptamine acetate was placed on the United States market as an anti-depressant. Soon after its release on the market, it was reported that etryptamine was associated with a high incidence of agranulocytosis, a potentially fatal condition. More recently, there were isolated reports of etryptamine being associated with the deaths of drug abusers in Germany, Spain and the United States of America.

3. Dependence potential

Animal drug discrimination studies indicate that etryptamine has subjective effects resembling MDMA. Self-administration studies indicate that etryptamine has a moderate dependence potential, which is lower than that of cocaine.

4. Actual abuse and/or evidence of likelihood of abuse

Information available from various sources indicates that there has been some abuse of etryptamine in Germany, Spain and the United States of America. Etryptamine is estimated to have a high abuse liability.

5. Therapeutic usefulness

In view of its association with serious adverse reactions such as agranulocytosis, the therapeutic usefulness of etryptamine is assessed to be very limited, if any.

6. Recommendation

Based on the available data concerning its pharmacological and toxicological profile, dependence potential and likelihood of abuse, the degree of seriousness of the public health and social problems associated with the abuse of etryptamine is assessed to be especially serious. On the basis of this and the assessment of its therapeutic usefulness, it is recommended that etryptamine be included in Schedule I of the Convention on Psychotropic Substances, 1971.

Flunitrazepam

1. Substance identification

Flunitrazepam (INN; CAS 1622-62-4), chemically 5-(o-fluorophenyl)-1,3-dihydro-1-methyl-7-nitro-2*H*-1,4-benzodiazepin-2-one, is also known as Absint; Darkene, Fluninoc, Flunipam, Flunita, Flunitrazepam-ratiopharm, Hypnodrom, Hipnosedon, Inervon, Narcozep, Parnox, Primun, Rohipnol, Rohypnol, Roipnol and Valsera.

2. Similarity to already known substances and effects on the central nervous system

Flunitrazepam has typical benzodiazepine effects, with a greater sedative-hypnotic potency than diazepam or chlordiazepoxide. Flunitrazepam binds with high affinity to central benzodiazepine receptors. Flunitrazepam is rapidly absorbed after oral administration. The elimination half-life of flunitrazepam following a single oral dose ranges between 9 to 25 hours in humans. Accumulation occurs with chronic administration.

3. Dependence potential

Drug discrimination, drug withdrawal and self-administration studies indicate that flunitrazepam has a dependence potential similar to other benzodiazepines. Rebound insomnia, which is considered a form of withdrawal from sedative-hypnotics, may be contributing to the tendency of continuing the medication. These data do not suggest any substantive difference between flunitrazepam and other benzodiazepine hypnotics.

However, drug preference studies in opioid users have shown that flunitrazepam and diazepam stand out from other benzodiazepines in terms of producing a strong positive reinforcing effect in these subjects.

Based on the above, flunitrazepam is estimated to have a moderate abuse potential which may be higher than other benzodiazepines. The rapid onset and longer duration of action, coupled with the strong sedative-hypnotic effects, may be contributing to its higher abuse potential.

4. Actual abuse and/or evidence of likelihood of abuse

Information available indicates that the non-medical use or abuse of flunitrazepam is widespread among drug abusers, particularly opioid and cocaine abusers. Flunitrazepam is reported to be the most widely abused benzodiazepine by opioid abusers in many large cities in Europe, Asia and Oceania. Flunitrazepam abuse is reported even in the United States of America where the drug is not marketed for therapeutic use.

Reported reasons for the abuse of flunitrazepam include potentiation of opioid effects, substitution for the opioid when it is difficult to obtain, and self-medication for opioid withdrawal. Oral intake is the most common route of administration of flunitrazepam but some abusers take the drug by intravenous injection or by snorting. Health problems associated with the abuse of flunitrazepam include deaths directly or indirectly related with the drug use, drug dependence, withdrawal syndrome, paranoia, amnesia and other psychiatric disorders.

Information on the extent of association of 37 benzodiazepines with illicit activities during the period 1984-1989, available to the 27th meeting of the WHO Expert Committee on Drug Dependence in 1990, clearly indicated a higher incidence of association with illicit activities of both diazepam and flunitrazepam in comparison with other benzodiazepines. At that time, however, the data were not evaluated in relation to drug availability. After an adjustment for the amounts manufactured and for potency, flunitrazepam further stands out in both seizures and the number of illicit cases involving the drug, whereas diazepam is no longer outstanding.

Information on drug involvement in illicit activities after 1990, received from governments in response to the WHO questionnaire in 1994, is limited, and does not allow a comparison among a large number of benzodiazepines. However, the recent report from Interpol and the increasing trend in the United States of America, despite the lack of licit medical supplies in that country, together with several recent reports showing flunitrazepam as being the main non-opioid drug abused by opioid abusers in major European cities, further substantiate its high abuse liability.

5. Therapeutic usefulness

Flunitrazepam is useful for the treatment of insomnia. It is also indicated as a pre-anaesthetic medication to assist in the induction and maintenance of anaesthesia. Flunitrazepam has a therapeutic usefulness similar to other benzodiazepine hypnotics, within the range from moderate to great.

6. Recommendation

Flunitrazepam has a greater likelihood of abuse than other benzodiazepines. Although there is some element of self-medication for opioid withdrawal, the abuse of flunitrazepam by opioid abusers complicates the clinical picture, leading to multiple drug dependence. Its abuse is prevalent also among youths and cocaine abusers. In addition to its oral and intravenous use, abuse by "snorting" has recently been reported. As yet, no other benzodiazepine has been reported as being abused by three different routes of administration; oral, nasal and intravenous. Flunitrazepam abuse has been associated with dependence and other behavioural problems. Illicit activities involving flunitrazepam are increasing even in the United States of America, where it is available illegally despite the lack of marketing for therapeutic use.

Based on the available data concerning its pharmacological and toxicological profile, dependence potential and likelihood of abuse, and paying particular regard to the above characteristics, the degree of seriousness of the public health and social problems associated with the abuse of flunitrazepam is assessed to have become substantial. On the basis of this and the assessment of its therapeutic usefulness, it is recommended that flunitrazepam be rescheduled into Schedule III of the Convention on Psychotropic Substances, 1971.

Mesocarb

1. Substance identification

Mesocarb (INN; CAS 34262-84-5), is chemically 3-(*α*-methylphenethyl)-*N*-(phenylcarbamoyl)sydnone imine, is also known as Pharmanocarb, Sidnocarb and Sydnocarb. Mesocarb has one asymmetric carbon atom in the molecule, so that two stereoisomeric forms and one racemate are possible.

2. Similarity to already known substances and effects on the central nervous system

Chemically, mesocarb is a sydnone imine having an amfetamine-like moiety in its molecule. Of the two optical isomers of mesocarb, only the levorotatory isomer exerts a stimulant effect on the central nervous system. This effect is significantly weaker than that of dexamfetamine. Mesocarb produces locomotor stimulation, anorectic activity, enhancement of conditioned reflexes, and shortening of the period of action of hypnotic agents. In addition, there are several pharmacological studies on mesocarb used in combination with other substances in animals, such as mesocarb-acetylsalicylic acid combination. Mesocarb has been reported to increase work capacity and improve cardiovascular function while maintaining normal oxygen consumption. Adverse reactions are similar to those of other CNS stimulants. Several studies in humans have shown that mesocarb increases resistance to environmental stress such as cold temperature, low gravity, and low oxygen levels in the air.

3. Dependence potential

Animal studies indicate that mesocarb has discriminative stimulus effects similar to CNS stimulants such as dexamfetamine and cocaine, as well as some reinforcing effects in monkeys, suggesting a low to moderate dependence potential.

4. Actual abuse and/or evidence of likelihood of abuse

There is some evidence to indicate that mesocarb is abused in sports, and its use has been banned by the International Olympic Committee.

Though reportedly discontinued, information from the International Narcotics Control Board indicated that large quantities of a pharmaceutical preparation containing mesocarb and acetylsalicylic acid were illegally exported to western Africa. Although epidemiological data are not available, it is believed that most, if not all, of the exported combination product was abused. On the basis of available information, mesocarb is assessed to have an appreciable abuse liability.

5. Therapeutic usefulness

Mesocarb is used in several countries, mainly in eastern Europe, as a stimulant to counteract acute intoxication by depressants; for the treatment of hyperactivity and nocturnal enuresis in children; and as an "energizer" to enhance resistance to environmental stress. The therapeutic usefulness of mesocarb is estimated to be within the range between little and moderate.

6. Recommendation

Although no epidemiological data are available on health problems associated with the actual abuse of mesocarb, mesocarb is abused in sports, and illicit activities involving mesocarb have been reported. Based on this and the available data concerning its pharmacological and toxicological profile, dependence potential and likelihood of abuse, the degree of seriousness of the public health and social problems associated with the abuse of mesocarb is assessed to be significant. On the basis of this and the assessment of its therapeutic usefulness, it is recommended that mesocarb be included in Schedule IV of the Convention on Psychotropic Substances, 1971.

Meth*cathinone*

1. Substance identification

Meth*cathinone* (CAS 5650-44-2), chemically 2-(methylamino)-1-phenylpropan-1-one, is also known as ephedrone and methyl*cathinone*. It has one chiral centre, so that two stereoisomeric forms and one racemate are possible.

2. Similarity to already known substances and effects on the central nervous system

Meth*cathinone* is the *N*-methyl derivative of cathinone, and is closely related to metamfetamine. Animal studies have shown that meth*cathinone* produces CNS stimulant effects similar to those produced by amfetamine, metamfetamine, cathinone and cocaine. Of the two optical isomers, the levorotatory form is more active.

3. Dependence potential

Drug discrimination and self-administration studies in animals indicate that meth*cathinone* has a dependence potential similar to central nervous system stimulants such as amfetamine and cocaine. Case reports and a study conducted in the United States of America on meth*cathinone* abusers also suggest that meth*cathinone* has a high dependence potential similar to that of metamfetamine.

4. Actual abuse and/or evidence of likelihood of abuse

Significant abuse of meth*cathinone* has been reported in Estonia, Latvia, the Russian Federation, and in some countries of the Commonwealth of Independent States as well as in the United States of America. Methcathinone is readily manufactured from ephedrine by oxidation. Meth*cathinone* is assessed to have a high abuse liability.

5. Therapeutic usefulness

Meth*cathinone* has not been marketed for therapeutic purposes. Its therapeutic usefulness is assessed to be very limited, if any.

6. Recommendation

Studies from the United States of America and the Russian Federation have confirmed that meth*cathinone* abuse results in adverse health effects similar to those associated with the abuse of metamfetamine, including fatal cases of acute intoxication. Illicit activities involving methcathinone, including clandestine manufacturing, are also reported widely.

Based on the available data concerning its pharmacological and toxicological profile, dependence potential and likelihood of abuse, and paying particular regard to the above characteristics, the degree of seriousness of the public health and social problems associated with the abuse of meth*cathinone* is assessed to be especially serious. On the basis of this and the assessment of its therapeutic usefulness, it is recommended that meth*cathinone* be included in Schedule I of the Convention on Psychotropic Substances, 1971.

Zipeprol

1. Substance identification

Zipeprol (INN; CAS 34758-83-3), chemically α-(α-methoxybenzyl)-4-(β-methoxyphenethyl)-1-piperazineethanol, is also known as Antituxil-Z, Cerm-3024, Chilvax, Delaviral, Dovavixin, Jactus, Eritos, Mirsol, Ogyline, Respilene, Respirase, Respirex, Sanotus, Santus, Silentos, Sousibim, Talasa, Tusigen, Tussiflex and Zitoxil. Zipeprol has three asymmetric carbon atoms in the molecule, so that eight stereoisomeric forms are possible.

2. Similarity to already known substances and effects on the central nervous system

In laboratory animals, zipeprol has been shown to have an antitussive activity weaker than codeine and comparable to dextromethorphan. Its pharmacological properties are different from those of opioid antitussives, such as codeine, in that zipeprol has anti-choliergic activities. It also does not produce respiratory depression, bile duct constriction or constipation, which are often associated with narcotic antitussives.

Unlike opioids, zipeprol is essentially devoid of analgesic activity, but at high doses, zipeprol acts as a weak opioid agonist. Zipeprol showed a bi-phasic effect in competing for binding sites in rat brain homogenates.

3. Dependence potential

In rats, lower doses of zipeprol amplify some opioid withdrawal manifestations whereas at higher doses it suppresses several morphine withdrawal symptoms. In the monkey, zipeprol suppresses morphine abstinence. Zipeprol is assessed to have a moderate dependence potential.

4. Actual abuse and/or evidence of likelihood of abuse

There have been a number of reports on the abuse of zipeprol from Brazil, Chile, France, Italy, Mexico, the Republic of Korea, Switzerland and the former Yugoslavia. These reports suggest that its sedative, hallucinatory and euphorigenic effects, and its ability to suppress some signs of opioid withdrawal at high doses, may be the reasons for its abuse. Over-the-counter distribution of zipeprol preparations may have contributed to its widespread abuse in some places. Taking this into account, zipeprol is assessed to have a moderate abuse liability.

Adverse health consequences of zipeprol abuse include seizures, hallucinations, confusion and amnesia. Dose escalation is not uncommon and fatal cases from acute intoxication were reported from several countries. The tablet form has been used for intravenous administration.

5. Therapeutic usefulness

A number of clinical studies have demonstrated the therapeutic efficacy of zipeprol for the treatment of cough. The therapeutic usefulness of zipeprol is assessed to be within the range between little and moderate.

6. Recommendation

Although zipeprol is a weak opioid agonist at high doses, its toxicity, hallucinogenic and other psychotropic effects constitute a significant element in its abuse. It is therefore appropriate to consider its control under the Convention on Psychotropic Substances, 1971.

Based on the available data concerning its pharmacological and toxicological profile, dependence potential and likelihood of abuse, the degree of seriousness of the public health and social problems associated with the abuse of zipeprol is assessed to be substantial. On the basis of this and the assessment of its therapeutic usefulness, it is recommended that zipeprol be included in Schedule II of the Convention on Psychotropic Substances, 1971.